Valproate Intoxication in a Patient With Blood Valproate Levels Within Therapeutic Range

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Valproate (valproic acid), a well-established anticonvulsant, is principally effective in bipolar disorder.[1–4] In addition, valproate has been used for the management of a range of psychiatric conditions, such as schizophrenia, personality disorder, anxiety, and agitation in dementia.[4–6]

The need for therapeutic drug monitoring of valproate in the treatment of epilepsy has been demonstrated. A plasma trough concentration exceeding 50 mg/L is advised in order to reach therapeutic effects on epilepsy, and trough levels exceeding 100–120 mg/L are associated with toxicity and occurrence of adverse events.[6–11] There is no clear concentration-response relationship for valproate in most psychiatric conditions. However, the range recommended in the literature for acute mania is 45–125 mg/L in adult patients and 65–90 mg/L in older patients; in maintenance therapy, blood levels of 55–115 mg/L have been recommended.[12–15] For this report, we used the ranges advised by our national guidelines[16]: 60–80 mg/L in maintenance therapy and 80–120 mg/L in acute episodes.

We present a case in which signs of valproate intoxication were clinically present, although the valproate trough concentrations were considered therapeutic (60–120 mg/L).

Case report. Ms A, a 78-year-old woman, was admitted to a geriatric psychiatry ward because of psychosis with manic features. The patient's psychiatric history revealed schizoaffective disorder (*DSM-5* criteria), and her somatic history included a stroke, metabolic syndrome, and chronic renal insufficiency. Psychiatric examination showed high speed in thinking, delusions, command auditory hallucinations, and a euphoric mood. Physical examination showed no abnormalities besides obesity and hyperkinesia due to haloperidol. Laboratory tests showed chronic renal insufficiency (clearance of 59 mL/min/1.73 m^2 [reference > 90 mL/min/1.73 m^2]).

Prescription of lithium carbonate was not the first choice due to lack of efficacy in the past and side effects (tremor and decline of renal function) in combination with the current reduced renal function. Ms A's manic psychosis was treated with valproate and haloperidol. Valproate was dosed according to the patient's body weight in a ratio of 20 mg/kg, which resulted in a daily dosage of 2,100 mg.

Two weeks later, she developed a fluctuating mental status with complaints of sedation, vertigo, and insecurity in walking with falling. Physical examination revealed no new abnormalities, and laboratory tests showed a serum albumin level of 26 g/L (reference, 35–50 g/L) and a plasma trough concentration of 91.9 mg/L (reference, 60–120 mg/L). In medication review by the pharmacist, a free protein unbound trough concentration level of valproate was determined at 34.7 mg/L (reference, 4–12 mg/L). Adjusting the daily valproate dosage to 600 mg resulted in a total valproate level of 49.9 mg/L and a free concentration of 6.1 mg/L (4–12 mg/L). The patient's vertigo, falling, and sedation resolved within 1 week, while the manic and psychotic features diminished.

This case demonstrates that valproate intoxication can be present despite a therapeutic dosage and a total valproate level within reference range. Symptoms of sedation, vertigo, and insecurity in walking could be attributed to a high protein-unbound plasma concentration of valproate.

Valproate is highly protein bound (mainly albumin) and limited primarily to the extracellular space, with a small (0.1–0.5 L/kg) volume of distribution (Vd). At levels exceeding 90 mg/L and in overdose, saturation of protein-binding sites occurs, resulting in a greater circulating free fraction of valproate and a larger Vd.[17] In elderly individuals, valproate elimination half-life is prolonged, which results from a greater Vd, probably due to an increased ratio of fat to lean tissue.[18,19] Concomitant therapy can influence valproate levels via induction or inhibition of cytochrome P450 and UDP-glucuronosyltransferase enzymes.[19–21]

Only unbound drug is pharmacologically active. High free plasma concentrations of valproate may lead to valproate toxicity and adverse effects. In most cases, it is sufficient, and more feasible, to measure total serum concentration of valproate, because there is a known fixed ratio between unbound and total valproate concentration. In most patients, the free fraction of valproate is about 10%. However, an increased free fraction of valproate may be present in some patient groups, resulting in drug toxicity even if the

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Table 1. Conditions That May Lead to Increased Concentrations of Free Valproate

Hypoalbuminemia (albumin < 30 g/L)
Older age
Pregnancy
Renal dysfunction (glomerular filtration rate < 50 mL/min/1.73 m^2)
Chronic liver disease
Concomitant medications that compete for albumin binding sites
Unexpected toxic effects while total valproate concentration is within therapeutic range

concentration of total drug is within therapeutic range[7,8,22,23] (Table 1).

In our opinion, measurement of free valproate concentrations is not needed routinely. However, as shown in our case, there are patients who have both therapeutic total valproate levels and intoxication symptoms due to a high free valproate level. We suggest considering determination of free valproate concentration in those patients who are at risk for developing toxic concentrations of free valproate[8,24] (see Table 1).

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